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Investigating thiol/disulfide homeostasis in acute migraine attack with aura

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Abstract
Aim: This study investigates thiol-disulfide hemostasis, which plays a role in the pathophysiology of migraine and is a new marker for oxidative stress in migraine with aura and healthy controls.
Material and methods: The study included 53 healthy controls and 60 patients who presented to Konya City Hospital Neurology Outpatient Clinic with headache and were diagnosed migraine with aura. First, written informed consent was obtained from patients and controls. Then, dynamic thiol-disulfide homeostasis was investigated following the automated spectrophotometric method in serum samples of migraine with aura and controls. Native thiol (SH), total thiol (TT), disulfide (SS), ischemia-modified albumin (IMA), disulfide/native thiol (SS/SH), disulfide/total thiol (SS/TT), and native thiol/total thiol (SH/TT) ratios of patients and control groups were calculated.
Results: Seven (11.7%) males and 53 (88.3%) females made up 60 migraine patients, and 5 (9.4%) males and 48 (90.6%) females made up 53-person control group. The mean age was 35.3 ± 10.1 years in the patient group and 36.2 ± 13.9 years in the control group. Native thiol concentration was 481.6 ± 53.2 µmol/L in the migraine group and 448.8 ± 70.5 µmol/L in the control group. Furthermore, total thiol concentration was 523.0 ± 55.3 µmol/L in the migraine group and 488.7 ± 72.3 µmol/L in the control group. Statistically significant differences were found between the groups regarding native and total thiol levels ($p < 0.001$). However, disulfide, IMA levels, and SS/SH, SS/TT, and SH/TT ratios were similar, and statistical differences between groups were not significant ($p>0.05$).
Discussion: Our results suggested evidence of increment in oxidative stress in migraine. Further research with a larger number of patients is needed to support the presence of oxidative stress in migraine.

Keywords
Migraine With Aura, Thiol/Disulfide Homeostasis, Oxidative Stress, Ischemia-Modified Albumin

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Introduction

Migraine is the most common neurological disease affecting a large population worldwide [1]. It is an episodic disease usually manifesting as nausea and/or recurrent severe headache with light and sound sensitivity [2]. The incidence of migraines in women is 2–3 times higher than in men [3]. In about one-third of individuals with migraines, transient neurological disorders called migraine aura sometimes or always persecute or accompany headaches [1, 3].

Although the pathophysiology of migraine is not well known, the most widely accepted theories are vascular, neurogenic, and cortically spreading depression hypotheses. In recent years, vascular and neuronal theories, which were combined into the neurovascular theory, have been accepted in the pathophysiology of migraine [4]. Additionally, recent studies on metabolism and mitochondrial dysfunction have suggested that migraine is partially due to an energy deficiency syndrome in the brain [5].

Reactive oxygen species (ROS), such as hydroxyl radicals, hydrogen peroxide, and superoxide radical anions, are produced as byproducts of normal metabolic processes, such as electron transport in mitochondria, host defense, or enzymatic reactions. Therefore, antioxidant defense systems in healthy organisms protect cells and tissues against these species [5, 6].

Oxidative stress causes an imbalance between the production of oxidants and their removal by antioxidants, producing oxidants to increase and accumulate in the body [6]. Oxidative stress is caused by excessive ROS production, mitochondrial dysfunction, impaired antioxidant system, or a combination of these factors [7]. When excessive ROS production exceeds the body's antioxidant capacity, damage occurs in cellular components, such as proteins, lipids, carbohydrates, and DNA [6-8].

Thiols, which contain the sulfhydryl (-SH) group, are an important component of the antioxidant cascade, eliminating ROS and other free radicals with enzymatic and non-enzymatic mechanisms [5, 9, 10]. Thiols react with ROS oxidation, reducing them; thus, protecting the organism from oxidative damage [10]. When oxidative stress increases, the oxidative reaction of thiols through oxidants forms reversible disulfide bonds. However, when the oxidative stress ends, disulfide bond structures are reduced to thiol groups; thus, maintaining the dynamic thiol/disulfide balance [10-12].

Dynamic thiol/disulfide homeostasis is critical for many physiological mechanisms, such as antioxidant protection, detoxification, signal transmission, apoptosis, regulation of the activity of enzymes, transcription factors, and cellular signal transmission mechanisms [11, 12].

Ischemia-modified albumin (IMA) is caused by oxidative stress or ischemia, resulting in reduced bonding capacity of transition metals, such as cobalt, copper, and nickel in the amino-terminal (N-terminal) region of the album [13]. This reduced binding capacity occurs primarily in cases of ischemia, hypoxia, acidosis, oxidative stress, and free iron and copper exposure [14].

Serum IMA levels were significantly higher in patients with acute coronary syndrome, pulmonary embolism, stroke and brain hemorrhage, mesenteric ischemia, and peripheral vascular disease [15].

Oxidative stress and thiol/disulfide homeostasis may be a factor in the pathogenesis of migraines and may be associated with excessive ROS, which can damage DNA. Furthermore, data on thiol/disulfide homeostasis were reported in studies in patients with migraine, but the results were controversial [9, 11, 16-18]. Therefore, our study investigates thiol-disulfide homeostasis, a potential new marker for oxidative stress, which is assumed to play a role in the pathophysiology of migraine.

Material and Methods

The study was conducted in Konya City Hospital Neurology Outpatient Clinic, where migraine with aura were diagnosed; Patients ≥18 years and older, without any other known chronic diseases, 60 patients without smoking, alcohol, and substance use and 53 healthy control individuals were prospectively evaluated.

Patients with systemic diseases (cardiovascular and cerebrovascular disease, diabetes, etc.), history of malignancies, smoking, alcohol and drug use, pregnancy, breastfeeding and prophylactic treatment for migraines in the last 6 months or taking chronic drugs were excluded from the study. Written informed consent was obtained from the patients and controls. All researchers have approved the ethical standards described in the Helsinki Declaration. Ethical approval was obtained from KTO Karatay University Clinical Research Ethics Committee.

Venous blood samples taken into biochemistry and EDTA tubes from the patients and control groups participating in the study were used. Blood samples were centrifuged at 1500 rpm for 10 minutes within 30 minutes after collection. Separated serum and plasma samples were aliquoted and stored at −80 °C until use.

The demographic characteristics of the participants, including gender, age, and residence addresses, were recorded. By performing physical examinations of the individuals, hemogram, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, sedimentation, and C-reactive protein (CRP) levels were determined.

Dynamic thiol-disulfide homeostasis in serum samples of migraine with aura and controls was investigated by automated spectrophotometric method developed by Erel and Neselioglu. Thiol/disulfide homeostasis tests were measured by the automated spectrophotometric method described by Erel and Neselioglu [12]. For short, disulfide bonds were first reduced to form free functional thiol groups with sodium borohydride. Unused reductant sodium borohydride was consumed and removed with formaldehyde to prevent reduction in DTNB (5,5'-dithiobis-(2-nitrobenzoic) acid), and all of the thiol groups, including reduced and native thiol groups were determined after reaction with DTNB. Half of the difference between the total and native thiols provides the dynamic disulfide amount. After the determination of native and total thiols, disulfide amounts, disulfide/total thiol percent ratios (SS/SH+SS), disulfide/native thiol percent ratios (SS/SH) and native thiol/total thiol percent ratios (SH/SH+) SS) were calculated.

The IMA levels were determined using the albumin cobalt binding test, a rapid colorimetric method developed by Bar-Or et al. [13], which is based on the binding ability of reduced cobalt ions (Co^{2+}) of human serum albumin due to ischemia. Briefly, 50 mL

of 0.1% cobalt (II) chloride (CoCl2) (Sigma-Aldrich, Germany) was added to the serum samples. After mixing, followed by 10 minutes of incubation to allow for albumin cobalt binding, 50 mL 1.5 mg/mL dithiothreitol was added. After mixing followed by 2 minutes of incubation, 1 mL of a 0.9% sodium chloride solution was added to reduce the binding capacity. The absorbance of samples was measured at 470 nm using a spectrophotometer. The results were expressed in absorbance units (ABSU) (kyn).

Hemoglobin (Hb), Hematocrit (Hct), Leukocyte (WBC), Platelet (PLT) values were studied on Sysmex XN-10™ Hematology System (Sysmex, Japan) automated blood count device. Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), creatinine (Kr) and CRP values were measured using Roche c702 chemistry autoanalyzer (Cobas 8000, Roche Diagnostics, Switzerland).

Sedimentation values were studied in Vision C autoanalyzer (Shenzhen YHLO Biotech, China). The value ranges of the tests were determined in accordance with the reference range of the Konya City Hospital Biochemistry laboratories where the measurements were made.

Statistical analysis

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) v.22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Results were presented as mean ± standard deviation, median, and minimum–maximum. Furthermore, the normality of the distribution of variables was confirmed with the Kolmogorov–Smirnov normality test. While comparing variables between groups, the Student's t-test or Mann–Whitney U test was used, depending on whether the statistical hypotheses were fulfilled or not. A p-value < 0.05 was considered statistically significant.

Results

Of the 60 migraine with aura included in the study, 7 (11.7%) were males, and 53 (88.3%) were females; 5 (9.4%) of the 53 control group were males, and 48 (90.6%) were females. The mean age of migraine group was 35.3 ± 10.1 years, and the mean age of the control group was 36.2 ± 13.9 years. Also, gender and age distributions were similar between the groups (p = 0.767, p = 708, respectively).

Table 1. Comparison of Thiol Disulphide Homeostasis and Ischemia motifine albumin (IMA) levels of the study and control groups

	Control	Migraine	
SH (µmol/L)	448.8±70.5	481.6±53.2	0.007[a*]
	467.7 (287.9-571.6)	476.2 (381.6-637.1)	
TT (µmol/L)	488.7±72.3	523.0±55.3	0.006[a*]
	508.3 (318.8-610.6)	516.0 (428.4-685.3)	
SS (µmol/L)	20.1±2.0	20.5±2.0	0.416[a]
	20.2 (17.2-24.5)	21.0 (17.3-24.2)	
SS/SH*100	4.4±0.7	4.3±0.6	0.585[b]
	4.5 (3.3-6.2)	4.2 (3.4-6.1)	
SS/TT*100	4.1±0.6	4.0±0.5	0.599[b]
	4.2 (3.1-5.5)	3.9 (3.2-5.5)	
SH/TT*100	91.7±1.4	92.0±1.1	0.258[b]
	91.5 (87.9-94.3)	92.3 (88.8-94.3)	
IMA (g/L)	0.792±0.013	0.790±0.014	0.524[b]
	0.790 (0.770-0.840)	0.790 (0.760-0.820)	

SH: Native thiol, TT: Total thiol, SS: Disulfide, IMA: Ischemia modified albumin. Results were presented as Mean ± Standard Deviation, median (%95 Confidence Interval for Mean Lower-Upper) value. [a]Student's t-test was performed, [b]Mann-Whitney U test was performed. *Statistically significant (p<0.05).

Native thiol (SH), total thiol (TT), disulfide (SS), IMA, disulfide/native thiol (SS/SH), disulfide/total thiol (SS/TT), and data on native thiol/total thiol (SH/TT) ratios are shown in Table 1.

The native-thiol concentration was 481.6 ± 53.2 µmol/L in the migraine group and 448.8 ± 70.5 µmol/L in the control group. The native-thiol levels of the migraine group were significantly higher than the control group. Also, there was a statistically significant difference between the groups regarding native-thiol levels (p=0.007).

The total thiol concentration was 523.0 ± 55.3 µmol/L in the migraine group and 488.7 ± 72.3 µmol/L in the control group. Total thiol levels in the migraine group were significantly higher than the control group. Total thiol levels in the migraine group were significantly higher than the control group (p=0.006).

Disulfide levels were 20.5 ± 2.0 µmol/L in the migraine group and 20.1 ± 2.0 µmol/L in the control group. The disulfide level was similar in both groups, and there was no statistically significant difference between the groups (p=0.416).

The SS/SH ratio was 4.3 ± 0.6 in migraine with aura and 4.4 ± 0.7 in the control group. The SS/SH ratio was similar in both groups, and there was no statistically significant difference between the groups (p=0.585).

The SS/TT ratio was 4.0 ± 0.5 in migraine group and 4.1 ± 0.6 in the control group. The SS/TT ratio was similar in both groups, and there was no statistically significant difference between the patient and control groups (p = 0.599). The SH/TT ratio was 92.0 ± 1.1 in migraine group and 91.7 ± 1.4 in the control group. There was no statistically significant difference between patient and control groups regarding SH/TT ratio (p=0.258).

IMA levels were 0.790 ± 0.014 in the migraine group and 0.792 ± 0.013 in the control group. There was no statistically significant difference between the migraine and control groups regarding IMA level (p=0.524).

Discussion

Thiols are essential molecules that can trigger redox reactions in organisms and remove them from the environment by reducing the number of oxidant molecules. Thiol metabolism plays a key role in the physiology of many central nervous system functions by contributing to transporting and signal transmission in cells. It also supports proteins' structural and functional integrity and normal enzyme activity [19, 20].

It has been suggested that some diseases, especially neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis, are associated with abnormal thiol-disulfide homeostasis [21, 22].

Therefore, our study investigated the dynamic thiol-disulfide homeostasis in migraine with aura attacks. Compared with the data obtained from the migraine group and the data obtained from the control group, we found that native and total thiol levels were significantly higher in the migraine group compared

to the control group.

Furthermore, there was no statistically significant difference between the groups regarding disulfide, IMA, disulfide/native thiol, disulfide/total thiol, native thiol/total thiol ratios.

Similar to our study, Gümüşyayla et al.'s [11] study conducted on 63 migraine (22 with and 41 without aura) and 50 healthy controls found that total and native-thiol levels were found in the migraine (497.11 ± 40.90; 462.10 ± 41.55 mmol/L) and control groups, respectively (477.51 ± 42.18; 437.39 ± 38.86 mmol/L) ($p<0.001$). There was no statistically significant difference between the two groups regarding disulfide, disulfide native-thiol ratio, disulfide total thiol ratio, and native thiol, total thiol ratio.

In 2020, Ersoy et al. [18] investigated IMA, total thiol, native thiol, and disulfide levels in 62 migraine and white matter lesions (with WML), 59 migraine and without white matter lesions (without WML), and 61 healthy controls. They found higher total and native-thiol levels in the non-WML group compared with the control and WML groups ($p<0.001$ for both). Disulfide levels were similar between the control and non-WML groups, whereas they were significantly lower in the WML group than the control and non-WML groups. They found that IMA levels were higher in the migraine group compared with the control group ($p<0.001$) and in the WML group compared with the non-WML groups ($p<0.001$). Furthermore, they did not find a significant relationship between thiol/disulfide, IMA levels, frequency and duration of attacks, pain severity, and migraine-related disability.

Contrary to our results, three more studies were conducted on thiol measurements in migraine, showing that total thiol levels were decreased in migraine compared with healthy volunteers. These results were attributed to the antioxidant properties of thiols [9, 16, 17].

A study by Eren et al. [9] in 141 migraine (77 with aura, 74 without aura) and 70 healthy controls in 2015 showed thiol levels to be significantly lower in migraine (604.2 ± 59.3 mmol/L) compared with healthy controls (670 ± 47.8) ($p<0.001$). However, there was no significant difference between migraine with aura (612.5 ± 56.3 mmol/L) and without aura (595.6 ± 61.4 mmol/L) ($p=0.152$).

Another study by Lucchesi et al. [16] showed 33 patients (30 females, 3 males) affected by chronic migraine and drug-overuse headache and 33 healthy controls. Also, they found statistically significantly lower total thiol groups in chronic migraine (0.26 ± 0.07) compared to controls (0.51 ± 0.08) ($p<0.001$).

A study by Gündüztepe et al. [17] investigated the effect of acupuncture on thiol-disulfide homeostasis and IMA levels in 22 migraine (with and without aura) and 25 healthy controls.

They found native-thiol levels to be significantly lower in the migraine group (327.16 ± 58.73 mmol/L) than in the control group (375.40 ± 45.20 mmol/L) ($p<0.05$). When migraine group before and after acupuncture were compared with the control group, there was a statistically significant difference in native-thiol levels between the groups ($p<0.05$). However, they found no significant difference in native-thiol levels before acupuncture compared with post-acupuncture in migraine group ($p>0.05$) [17].

They found that the total thiol levels in the migraine group (397.80 ± 56.40 mmol/L) were significantly lower than the control group (437.14 ± 49.70 mmol/L). In addition, they found statistically significant differences in total thiol levels in migraine group before and after acupuncture compared with the control group ($p<0.05$). However, they did not detect a significant difference between the post-acupuncture groups' total thiol levels compared with the pre-acupuncture groups ($p>0.05$) [17].

Furthermore, they found that total thiol, native thiol, dynamic disulfide bond levels, and IMA levels were correlated with migraine attack frequency, pain severity, and migraine type. They suggested that thiol-disulfide homeostasis and IMA levels may play a role in the etiology and severity of migraine and that acupuncture treatment will reduce oxidative stress in migraine [17].

Studies have revealed that thiols are mostly antioxidant molecules, but they sometimes act as pro-oxidant molecules because they are affected by the organism's physiological state [9, 24]. The high thiol levels detected in our study may be related to the pro-oxidant nature of thiols [11, 18]. Although thiols are the most important antioxidant molecules, in the case of oxidative stress, the concentration of sulfur-containing amino acids can change their structure and gain pro-oxidant properties according to the antioxidant properties of the proteins and enzymes involved in the structures. The oxidative stress level of the organism determines the antioxidant and pro-oxidant effects of thiols. This balance is dynamic and may change according to the organism's state [11, 18, 23].

Pro-oxidant properties and increased homocysteine and cysteine levels of thiol-containing molecules have been reported in some studies. Additionally, homocysteine and cysteine levels increase in cardiovascular disease, cerebrovascular disease, and renal ischemia; oxidative stress plays a role in the pathogenesis of these diseases [11, 24].

Conclusion

We found increased total and natural thiol levels in migraine with aura attacks compared with healthy controls. These results support the idea that thiols affect the physiological state of an organism and, in this case, act as pro-oxidant molecules as they are dynamic molecules. Conclusively, oxidative stress plays a role in the pathogenesis of migraine. However, considering individual differences, further comprehensive studies with larger sample sizes are needed.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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